Primary CNS Lymphoma

Las Vegas-- March 11, 2016
Disclosures

- Advisory Board: Seattle Genetics, Forty-Seven, Inc.
- I will discuss off-label use of temozoloide, lenalidomide and ibrutinib.
Outline

- Demographics
- What do we know about the unique markers/makeup of PCNSL?
- PCNSL -- prognosticating outcome
- Presentation
- Workup
- Treatment (usual vs. special circumstances)
- AutoSCTx in CR1 or not?
- Treatment of Relapsed disease
Demographics

- 3% of primary cerebral tumors
- 2-3% of all cases of NHL.
- SEER data show incidence may be increasing among patients >65, with pts >75 having the highest incidental risk.
- 1900 new cases per year in U.S.
- Limited prospective and/or randomized data to guide its therapy.
- Historically associated with a poor prognosis.
- Accumulation of recent prospective phase I/II results, and retrospective series demonstrate reproducible improvements in outcomes for patients with PCNSL and SCNSL.
Risk Factors

- Acquired or congenital immunodeficiency states (WAS, AT, SCID, CVID—4% lifetime risk)
- Renal transplant 1-2% lifetime risk
- 2-7% cardiac, lung, liver transplant—association with T-cell specific immunodeficiency (mycophenolate)
- AIDS-defining illness, assoc. with very low CD4 count (<50 cells/μL)—nearly 100% assoc w/EBV
Incidence Trend PCNSL 1980-2008

Rate by gender/race

Rate by age at dx

Rel. survival by age group

By gender/race for <50yo

By gender/race for >50
The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma.
The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma.
PCNSL must be considered a “whole brain disease”
Characteristic radiographic features of PCNSL on magnetic resonance imaging.

Histology

- **DLBCL CD20+ 95%**
- T-cell PCNSL 2%, Burkitt, LB, intraparenchymal MZL.
- 20% present with intra-ocular involvement.
  - IOL progresses to CNSL in 80% cases, mandating staging procedures commensurate with risk.
Schematic representation of our hypothesis, developed to explain the histogenesis of PCNSL, taking into consideration the time of B-cell arrest and the corresponding antigen expression.

### Table: Germinal Center vs. After GC

<table>
<thead>
<tr>
<th></th>
<th>Germinal center</th>
<th>After GC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>CD10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bcl-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUM1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCNSL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic DLBCL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CD10: 10-20%
- Bcl-6: 50-80%
- MUM1: 95%

Sophie Camilleri-Broët et al. Blood 2006;107:190-196

©2006 by American Society of Hematology
BCL6 expression influences outcome in patients treated on CALGB 50202
PCNSL

- Late germinal center or post-germinal center lymphoid cells that show very distinct characteristics that separate them from nodal DLBCLs.
ABC-like immunophenotype

- 95% stain for MUM-1, consistent with overlapping features of germinal center and activated B-cell phenotypes.
Comparison of overall survival rates for patients with PCNSL or systemic DLBCL expressing ABC phenotypes.

Camilleri PCNSL cohort 83 patients, OS compared to 240 patients with systemic DLBCL –96.4% ABC

(previously presented by Rosenwald et al, NEJM. 2002;346: 1937-1947.)

Sophie Camilleri-Broët et al. Blood 2006;107:190-196
Molecular genetics

- 3 genome wide analyses using whole genome sequencing
- Identify alterations of NF-kB pathways, especially through somatic mutations of MYD88 (leu265pro 38-50%) and CD79B (20%)
  - Bruno et al. Oncotarget 2014;5:5065-5075
  - Vater et al. Leukemia 2014
Oncogenic survival signaling components in PCNSL

Activation of TLR/MYD88 pathway may directly contribute to pro-survival signaling directly via NFkB as well as via the enhanced production of IL-10 which itself contributes to survival signals via the JAK/STAT pathway.
Presentation

- Neuroanatomic lesion location determines clinical presentation
  - >60% have cognitive, motor or constitutional sx
  - 30% have visual sx at presentation
  - 20% have seizures.
  - Concomitant leptomeningeal disease 15-20% typically asx.
CT/MRI findings suspicious for PCNSL

Withhold corticosteroids
Chest x-ray, CT: chest, abdomen, pelvis, testicular ultrasound
CBC, HIV, LDH

SLE and lumbar puncture with cytology and flow cytometry

+ Cells in vitreous
  Vitrectomy
  - Lymphoma
    Brain biopsy
    - PCNSL
      Diagnosis — appropriate therapy
    + PCNSL
  + Lymphoma

+ CSF lymphoma

- CSF and SLE
  Brain biopsy
  + PCNSL
  Diagnosis — appropriate therapy
  - PCNSL

Liver function tests
Creatinine clearance
Spinal MRI
Assess cognitive function (MMSE)

Corticosteroids if necessary for symptom control
Definitive treatment of PCNSL
Prognosis

IELSG parameters:
- Age >60*
- ECOG >1
- LDH > ULN
- High CSF protein
- Tumor location in BG, periventricular, brainstem/cerebellum

<table>
<thead>
<tr>
<th># RF</th>
<th>2Y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>80%</td>
</tr>
<tr>
<td>2-3</td>
<td>48%</td>
</tr>
<tr>
<td>4-5</td>
<td>15%</td>
</tr>
</tbody>
</table>
Treatment: Surgery

Aggressive surgery is generally not recommended, however:

PFS (A) and OS (B) by extent of resection: gross total resection vs subtotal resection vs biopsy in the primary eligibility population of 526 patients

(PFS: P = .005 for biopsy vs gross or subtotal resection, P = .023 for gross total vs subtotal resection; OS: P = .024 for biopsy vs gross or subtotal resection, P = .218 for gross total vs subtotal resection)
Whole Brain Irradiation

- Utility is limited by
  - Insufficient local control of disease
  - Dissemination of cells within the CSF circulation (outside radiation field)
  - Detrimental effects of XRT on brain function.
  
  - Single agent therapy with WBRT ORR 90%, but OS 11.6 mo with >60% of patients with progression within the irradiated field.
Neurotoxicity of WBRT

- Incontinence, gait, memory disturbances
- Pt older than 60 y more vulnerable (many require custodial care to manage).
- Lower doses– prophylactic WBRT at 30Gy also produces significant neurotoxicity.
Radiation Toxicity

• Acute Adverse Effects- alopecia, erythema and dry desquamation of the scalp. Some experience fatigue, headache and inflammation of the external auditory canal or middle ear.

• Patients requiring treatment of the eye are likely to experience conjunctival irritation and dry eye.

• These acute effects typically resolve within 6 – 8 weeks of completion of WBRT.
Radiation Toxicity

• Late adverse effects: neurocognitive decline, sensorineural hearing loss, permanent alopecia
• Those whose eyes are treated- cataracts, chronic dry eye
• The risk of neurocognitive dysfunction increases with age, total RT dose and co-administration of chemotherapy
# Treatment Regimens for PCNSL

<table>
<thead>
<tr>
<th>Study (#pt)</th>
<th>Regimen</th>
<th>ORR</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBRT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson et al, 1992 (n=14)</td>
<td>WBRT 40GY +20Gy boost</td>
<td>100%</td>
<td>MA</td>
<td>12.2</td>
</tr>
<tr>
<td><strong>MTX monotx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batchelor, 2003 (N=23)</td>
<td>MTX 8gm/m2</td>
<td>74%</td>
<td>12.8mo</td>
<td>&gt;23</td>
</tr>
<tr>
<td>Herrlinger, 2005</td>
<td>Mtx 8gm/m2</td>
<td>35%</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td><strong>Combined modality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferreri 2009</td>
<td>Mtx 3.5gm/m2 +WBRT</td>
<td>41%</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Ferreri 2009</td>
<td>Mtx 3.5gm/m2 +HIDAC +WBRT</td>
<td>69%</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>DeAngelis 2002</td>
<td>MPV + Itmtx +WBRT (45Gy)+HIDAC</td>
<td>94%</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>Shah, 2007</td>
<td>R-MPV+HIDAC+WBRT (23Gy)</td>
<td>93%</td>
<td>&gt;37</td>
<td>40</td>
</tr>
<tr>
<td><strong>Intensive chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illerhaus, 2008</td>
<td>Mtx 8gm/m2 +HIDAC+BCNU/TT(ASCT)</td>
<td>85%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rubenstein, 2013</td>
<td>MT-R +EA</td>
<td>77%</td>
<td>52</td>
<td>NR</td>
</tr>
</tbody>
</table>
Progress in the treatment of PCNSL. Comparison of outcomes for newly diagnosed PCNSL in 2 multicenter cooperative group clinical trials.

Mtx 2.5mg/m2, vcr, procarb, IT mTX, Dex, hyperfractionated WBRT 45Gy, HIDAC x 2

What dose of MTX to use?

- Optimal doses have not been defined
  - Doses > 1gm/m2 achieve tumoricidal levels of mtx in brain parenchyma. (Skarin et al, BLOOD 1977)
  - Retrospective analysis of PCNSL outcomes at MSKCC demonstrate that elimination of IT MTX did not affect outcome in pts treated at a target dose of 3.5g/m2. (Khan et al, J Neuro-oncol, 2002)
  - 8gm/m2 produces higher cytotoxic levels in serum and csf than IT mtx (Glantz et al, JCO 1998)
Progress in the treatment of PCNSL. Comparison of outcomes for newly diagnosed PCNSL in 2 multicenter cooperative group clinical trials.

Mtx 2.5mg/m2, vcr, procarb, IT mTX, Dex, hyperfractionated WBRT 45Gy, HIDAC x 2

Protocol schema.

**Remission Induction Therapy** (4 cycles)

- **ReStAge**
  - CR, CRu → Consolidation
  - PR, SD, PD → Off-Protocol

**Remission Induction Therapy: MT-R (14-day cycle)**

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methotrexate 8 grams/m² IV over 4 hrs</td>
</tr>
<tr>
<td>2</td>
<td>Leucovorin 100 mg/m² every 6 hrs, until methotrexate &lt; 0.05 mM</td>
</tr>
<tr>
<td>3</td>
<td>Rituximab 375 mg/m² IV cycles 1 through 6</td>
</tr>
<tr>
<td>7-11</td>
<td>Temozolomide 150 mg/m² PO (odd cycles only)</td>
</tr>
</tbody>
</table>

**Consolidation Therapy: EA**

<table>
<thead>
<tr>
<th>Day 1-4</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Etoposide 40 mg/kg continuous IV over 96 hrs</td>
</tr>
<tr>
<td>1-4</td>
<td>Cytarabine 2 gm/m² IV over 2 hrs every 12 hrs × 8 doses</td>
</tr>
</tbody>
</table>

James L. Rubenstein et al. JCO 2013;31:3061-3068
Clinical prognostic variables and their relationship to progression-free survival (PFS); median PFS survival was 2.4 years

James L. Rubenstein et al. JCO 2013;31:3061-3068
BCL6 expression is associated with short time to progression (TTP) and overall survival (OS) in patients with primary CNS lymphoma (PCNSL) treated in the 50202 study.

James L. Rubenstein et al. JCO 2013;31:3061-3068
<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-PCNSL-SG1</td>
<td>HD-MTX-based induction +/- WBRT consolidation</td>
<td>Thiel et al. (81)</td>
</tr>
<tr>
<td>IELSG-20</td>
<td>HD-MTX +/- HD-Ara-C- &gt; WBRT consolidation</td>
<td>Ferreri et al. (80)</td>
</tr>
<tr>
<td>IELSG-32</td>
<td>Myeloablative vs. WBRT consolidation</td>
<td>Accrual complete</td>
</tr>
<tr>
<td>Alliance 51101</td>
<td>Intensive vs. myeloablative consolidation</td>
<td>Active</td>
</tr>
<tr>
<td>PRECIS</td>
<td>Myeloablative vs. WBRT consolidation</td>
<td>Active</td>
</tr>
<tr>
<td>Matrix/IELSG43</td>
<td>Intensive vs. myeloablative consolidation</td>
<td>Active</td>
</tr>
</tbody>
</table>

CALGB (Alliance) 51101 compares dose-intensive consolidation with infusional etoposide plus high-dose cytarabine (EA) with high-dose chemotherapy (BCNU plus thiotepa), supported by autologous stem cell transplant (7). The MATRIX/IELSG43 evaluates high-dose chemotherapy, BCNU plus thiotepa supported by autologous stem cell transplant in comparison to a dose-intensive consolidation regimen consisting of dexamethasone, etoposide, carboplatin and ifosfamide. HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy; Ara-C, cytarabine.
## Reported studies for PCNSL-AutoHSCT

<table>
<thead>
<tr>
<th>Ref.</th>
<th>#p</th>
<th>Tx line</th>
<th>Therapy (induction/intensification)</th>
<th>ASCT cond.</th>
<th>WBRT</th>
<th>Outcome</th>
<th>Neurotox</th>
<th>Medican Followup (mo)</th>
<th>TRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubenstein</td>
<td>22</td>
<td>Salvage</td>
<td>EA</td>
<td>TT/Bu/Cy</td>
<td>N</td>
<td>3-y OS 64%</td>
<td>32</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td>Illerhaus</td>
<td>43</td>
<td>Salvage</td>
<td>EA</td>
<td>TT/Bu/Cy</td>
<td>N</td>
<td>2-y OS 45%</td>
<td>5</td>
<td>36</td>
<td>7</td>
</tr>
<tr>
<td>Bromberg</td>
<td>6</td>
<td>First-line</td>
<td>MBVP</td>
<td>BEAM</td>
<td>Y</td>
<td>2-y OS 40%</td>
<td>33</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Korfel</td>
<td>25</td>
<td>First-line</td>
<td>MBVP</td>
<td>BEAM</td>
<td>Y</td>
<td>4-y OS 64%</td>
<td>8</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>Wieduwilt</td>
<td>30</td>
<td>First-line</td>
<td>HD-MTX/AraC/TT</td>
<td>BCNU/TT</td>
<td>Y</td>
<td>5-y OS 69%</td>
<td>17</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>Schabet</td>
<td>13</td>
<td>First-line</td>
<td>HD-MTX/AraC/TT</td>
<td>BCNU/TT</td>
<td>Y</td>
<td>3-y OS 77%</td>
<td>0</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Cingolani</td>
<td>23</td>
<td>First-line</td>
<td>HD-MTX/7-arac</td>
<td>Bu/TT</td>
<td>Y</td>
<td>2-y OS 48%</td>
<td>39</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Lai</td>
<td>28</td>
<td>First-line</td>
<td>HD-MTX/araC</td>
<td>BEAM</td>
<td>N</td>
<td>2-y OS 55%</td>
<td>0</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td>Shenkler</td>
<td>7</td>
<td>First-line</td>
<td>HD-MTX/araC</td>
<td>TT/Bu/Cy</td>
<td>N</td>
<td>3-y OS 50%</td>
<td>0</td>
<td>28</td>
<td>14</td>
</tr>
</tbody>
</table>
Lenalidomide is highly active in recurrent CNS lymphoma

- Lenalidomide active in aggressive NHL esp ABC subtype
- Case report in 2011- efficacy of lenalidomide in ocular lymphoma
- Phase 1 trial of Lenalidomide in CNS NHL

Rubenstein et al
Methods

- Determine safety and efficacy of 3 dose levels of Lenalidomide in refractory CD20+ CNS lymphoma
- Determine CSF penetration of Lenalidomide
- Feasibility of combined IT and IV rituximab
- Effect of lenalidomide on tumor microenvironnement
Results

- 9 patients on phase 1 (7 PCNSL, 2 SCNSL)
- 8 evaluable
- 6/8 had response at 1 month of therapy, 2 CRs, 1 PR in brain NHL, 1 CR of CSF NHL and 1 CR and 2 PR of intraocular lymphoma
- 3 maintain response to mono therapy at > 6 months and 2 beyond 1 year.
Results

• Independent cohort of 10 patients received lenalidomide maintenance after initial salvage therapy
• Median fu is 18 months
• 5 pts have durable response after 2 years
• Lenalidomide levels detected in ventricular CSF in 4 patients, 12-15 hours after a 20 mg dose
• Metabolic profiling suggested CSF lactate correlated with response
Lugano 2015
Phase I/II study of TEDDI-R in PCNSL

- Temazolomide, etoposide, doxil, dex, ibrutinib and rituximab with IT cytarabine
- MTX excluded due to interaction with ibrutinib in vivo
Additional abstracts of interest: TEDDI-R for CNS lymphoma
Dunleavy, Lai, Roschewski, Brudno, Widemann, Pittaluga, Jaffe, Lucas, Stevenson, Yuan, Harris, Cole, Butman, Little, Staudt, and Wilson

Dose Adjusted-TEDDI-R

- Temozolomide 100 mg/m²/day IV days 2 to 5
- Etoposide 50 mg/m²/day IV days 2 to 5
- Doxil 50 mg/m² IV day 2
- Dexamethasone 10 mg/m² BID PO days 1 to 5
- Ibrutinib (560-TBD mg) PO days 1-10 (days -14 to 5 on cycle 1)
- Rituximab 375 mg/m² IV on days 1 and 2
- Pegfilgrastim 6mgs on day 6
- Cytarabine 70 mg IT or ICV on days 1 and 5 of cycles 2 to 6

No MTX

Repeat cycle q21 days x 6
Methods

- Untreated or R/R PCNSL
- Ibrutinib 560 mg PO daily for 14 days
- followed by brain MRI/PET
- Followed by DA-TEDDI-R every 21 days x 6 cycles
- Plasma and CSF PKs of Ibrutinib and its metabolite PCI-45227
6 enrolled so far
6 completed ibrutinib
4 completed at least 2 cycles of chemo
Pk in 4 patients have shown CSF penetration of ibrutinib and its metabolite
Tumor improvement seen in 5/6 patients with ibrutinib alone
Results and conclusions

- 51 (4%) developed CNS relapse at a median time of 9 months
- CI of CNS relapse at 2 years was
  - Low risk - 0.5%
  - Intermediate risk - 2.5%
  - High risk – 12.3% - (85/235 of high risk received CNS prophylaxis, IT alone 22%, systemic 31%, both 47%). Number of CNS events was the same with or without prophylaxis i.e 12%
Plasma/CSF Concentration x Time Profile
(Mean±SD)

Patients 1-6: 560mg dose

Ibrutinib and its active metabolite achieve meaningful CSF concentrations
RESULTS: Case Example Patient 4 (52 yo) – DA-TEDDI-R

Ibrutinib → DA-TEDDI-R
Newly diagnosed primary CNS lymphoma

Adequate renal function? (GFR > 30)

Combination chemotherapy with HD-MTX

- Stable or progressive disease
  
  CR / CRu / significant partial response

  Consolidation therapy
  • WBRT
  • Non-myeloablative chemotherapy
  • ASCT with thiotepa-based regimen (preferred)

  Surveillance

  CR / CRu / significant partial response

  Salvage therapy with CNS-penetrative agents

  Stable or progressive disease

  Palliative WBRT

  Surveillance

Relapse or disease progression

Salvage therapy (including HD-MTX if previous response and adequate GFR) vs. WBRT.

- CR / CRu / significant partial response
  
  ASCT with thiotepa-based regimen (if not previously received) and clinically eligible or WBRT (if not previously received)

- Stable or progressive disease
  
  Palliative WBRT if not previously done or best supportive care

Combination therapy without HD-MTX

- CR / CRu / significant partial response
  
  Consolidation therapy
  • WBRT
  • Non-myeloablative chemotherapy

  Surveillance

- Stable or progressive disease
  
  Palliative WBRT

CR / CRu / significant partial response

Stable or progressive disease

Yes

No